45 Safety, tolerability and efficacy of multiple, rising doses of aerosolized Moli1901 in CF patients

F. Ratjen[1,2], F. Stehling[2], K. Starke[3], H. Brunar[4], T. Laliberte[5], R. Widmann[4], L. Molina[5], H. Grasemann[1,2]. [1]*Hospital for Sick Children, Toronto, Canada;* [2]*Children's Hospital, University of Essen, Germany;* [3]*Ruhrlandklinik Essen, Germany;* [4]*AOP Pharmaceuticals, Wien, Austria;* [5]*Lantobi Inc, USA*

Affiliation, Country

Moli1901 activates a Ca2+-dependent alternative Cl–channel with the potential to bypass dysfunctional CFTR. In this phase IIa single center, placebo controlled, double-blinded study we assessed safety and tolerability of Moli1901 in 3 doses (0.5, 1.5 and 2.5 mg/d) versus placebo (normal saline) once daily for 5 days administered by inhalation (PARI LC Plus). Within each cohort of 8 patients, 6 received Moli1901 and 2 placebo. Patients included were ⩾16 years of age with a FEV1 > 60% predicted. Exclusion criteria were ABPA, B. cepacia infection and severe liver disease. The study involved 8 clinic visits over a period of 4 weeks to assess for adverse events, pulmonary function tests (PFTs), O_2-saturation and quality of life. A significant adverse event was defined a priori as a decline of FEV1 ⩾20% from baseline accompanied by symptoms. 3 patients (one in each cohort) had a decrease in FEV1 > 20% following the first inhalation. Treatment was discontinued in one of these patients because of wheezing; however FEV1 returned to baseline on the following day. Subsequent inhalations in the other two patients did not result in a persistent decline in FEV1. All other patients tolerated inhalation well. The median change FEV1 from day 1 to day 5 was –2.5% in the placebo group, 2% in the 0.5 mg/d, 6% in the 1.5 mg/d and 7% in the 2.5 mg/d group. Although this trial was not primarily designed to show efficacy, the differences between treatment groups were significant (Kruskal-Wallis test, $p = 0.03$). Post-hoc paired comparisons demonstrated a significant difference between the 2.5 mg/d group and placebo (Wilcoxon test, $p = 0.01$), but not for the other treatment groups. No significant changes were observed in other lung function parameters and O_2-saturation. These results support the further investigation of Moli1901 in CF patients.

46* Inhaled dry powder mannitol (Bronchitol) improves FEV1 in Cystic Fibrosis

B. Charlton[1], A. Lassig[1], CF-201 Study Investigators[2]. [1]*Pharmaxis Ltd, Frenchs Forest, NSW, Australia;* [2]*CF-201 study sites, Australia*

Aims: Bronchitol, an osmotic agent, has been shown to increase mucociliary clearance. We determined the effect of 2 weeks' treatment with Bronchitol on lung function, efficacy and safety parameters in patients with CF.

Methods: Patients with known CF, age >8 and FEV1 40–80% predicted were enrolled. The blinded, controlled, cross-over study design involved 2 weeks treatment with inhaled Bronchitol (420 mg bd) or control, 2 weeks washout, and then 2 weeks on the alternative treatment. Endpoints were FEV1 (primary), FEF25–75, FVC, FEV1/FVC, PEFR, QoL questionnaire (CFQ), symptom questionnaire, physical signs, sputum microbiology and safety profile.

Results: Thirty nine patients of both genders and average age 19 (8–48) years with a baseline FEV1 of 65±13% predicted were randomized to treatment. Half the patients used concomitant Pulmozyme treatment. Primary endpoint: FEV1 increased 7±2% on Bronchitol (121±33 mls) and unchanged on control ($p < 0.01$ vs control). Secondary endpoints: FEF25–75 increased 15.5±5% on Bronchitol (0.15±0.05 L/sec) and unchanged on control ($p < 0.01$ vs control), FEV1/FVC ratio increased by 2.2±1.1% on Bronchitol ($p < 0.05$ vs control), FVC increased 4.6±1.6% on Bronchitol (NS). Symptoms improved on Bronchitol compared with control ($p < 0.05$). Abnormal chest sounds improved on Bronchitol (vs control $p < 0.05$). CFQ domains were all improved on Bronchitol but did not reach statistical significance. The treatment effects were independent of concomitant Pulmozyme use. Sputum microbiology was unchanged overall on either treatment and no serious or significant adverse events were related to treatment with Bronchitol.

Conclusions: Bronchitol was well tolerated and efficacious during two weeks administration in patients with CF. Longer term studies are warranted.

47* Denufosol tetrasodium inhalation solution: results from two phase 2 trials in CF patients with mild to moderate lung disease

L. Smiley[1], A. Rossi[1], D. Mathews[1], J. Engels[1], A. Schaberg[1], D. Kellerman[1], C. Shaffer[1], R. Deterding[2]. [1]*Inspire Pharmaceuticals, Inc., Durham, NC;* [2]*University of Colorado, Denver, CO, USA*

Aims: Denufosol, a selective $P2Y_2$ receptor agonist, is designed to provide potential benefit to CF patients through its actions on enhancing mucociliary clearance and has been studied in several Phase 2 trials.

Methods: Two 28-day, placebo-controlled, randomized, multi-center studies were conducted in a total of 161 CF patients. The first study enrolled patients with mild CF with FEV_1 ⩾75% of predicted normal while the second study included patients with FEV_1 60%-90%. Consistent trends with respect to the benefit of denufosol as an early intervention treatment (i.e., in 130 patients with FEV_1 ⩾75% of predicted normal) from these two studies is presented below.

Results: Cough was consistently among the most frequently reported AE in denufosol vs placebo recipients [47% vs 52% (first study); 37% vs 29% (second study), respectively]. Patients treated with denufosol (active doses combined) had better lung function at the end of the study as compared to placebo [differences from placebo in percent change from baseline for FEV_1 and $FEF_{25\%–75\%}$ were 4.0% and 8.3% (first study); 2.4% and 5.9% (second study), respectively]. Overall, fewer pulmonary exacerbations were reported in the denufosol group vs placebo [4% vs 10% (first study); 4% vs 7% (second study), respectively].

Conclusions: Doses of denufosol up to 60 mg given three times daily were generally well tolerated. Although these studies were not designed as efficacy studies, denufosol had favorable effects on lung function and exacerbation rates over 28 days in patients with mild lung function impairment. Denufosol development will advance into longer term Phase 3 studies.

48 The impact of azithromycin on moderately severe adult Cystic Fibrosis patients

Z.E.K. Hoare, J.C. Dewar. *Nottingham Adult CF Centre, Nottingham City Hospital (NCH), Nottingham, UK*

Introduction: Macrolide antibiotics are becoming an accepted anti-inflammatory treatment in Cystic Fibrosis (CF) [1]. The largest trial (n = 185) showed a small improvement in FEV1, plus a significant reduction of in-patient days and intravenous antibiotics [2]. Most trials have been small and so the role of macrolides remains unclear. We applied stringent criteria for use at the adult CF unit, NCH, in order to audit efficacy, as follows: FEV1 < 50%, frequent exacerbations or a rapid deterioration in clinical state.

Methods: A retrospective audit of case notes on the first twenty patients at NCH commenced on azithromycin, 250 mg, thrice weekly. Impact on FEV1, BMI (body mass index) and number of exacerbations per 12 months was assessed. Change in FEV1% predicted; BMI; and number of exacerbations for 12 months pre-azithromycin and six months post-azithromycin were compared using a paired t-test. Potentially confounding factors including major changes to treatment were noted.

Results: Population demographics: average age 29, FEV1 predicted 47%, and BMI 19.9. There was a significant average improvement in FEV1 predicted of 19% ($p < 0.045$ CI 0.004–0.358) during the first 6 months of treatment. Average BMI improved by 4.1% ($p = 0.087$ CI 0.012–0.159) and the average number of exacerbations was reduced by 17% ($p = 0.118$ CI 0.002–0.012). There were no adverse events.

Discussion:

- Azithromycin appears to improve FEV1 and BMI, reducing infective exacerbations in our moderately severe patients.
- Whilst numbers are small and data retrospective, this audit gives a clear picture of what is actually happening in real-time clinical practice in an adult CF unit.
- A national trial is required to more carefully delineate the role of azithromycin in CF.

References

[1] Schoni MH. Swiss Med Wkly. 2003 May 31; 133(21–22) 297–301.
[2] Saiman L et al. JAMA 2003: 290: 1749–76.